REMARKS

Claims 60-77 were pending in the instant application as of the issuance of the Office Action dated August 20, 2007. According to the foregoing amendments, claims 60, 62 and 70 have been amended, claims 63-67, 69, 73-75 and 77 have been cancelled without prejudice to the prosecution of these claims in this or a subsequently filed application, and new claims 78-86 have been added. Accordingly, after the amendments presented herein have been entered, claims 60-62, 68, 70-72, 76 and 78-86 will remain pending in this application.

Support for the amendments to the claims and the introduction of new claims may be found throughout the specification and in the claims as originally filed. Specifically, support for the amendments to claim 60 can be found throughout the specification at, for example, page 10, line 23-25 and page 36, lines 11-12. Support for the amendments to claim 70 can be found throughout the specification at, for example, page 7, lines 8-10; page 8, lines 8-11; page 11, lines 7-10; page 14, lines 17-18; page 17, lines 3-5; page 25, lines 10-14; page 33, line 10 to page 34, line 14 and page 36, lines 11-12. Support for new claims 78 and 79 can be found throughout the specification at, for example, page 33, line 10 to page 34, line 14 and page 36, lines 11-12. Lastly, support for new claims 80-86 can be found throughout the specification, for example, at page 11, line 30 to page 13, line 15, and in the claims as originally filed.

No new matter has been added by the amendments to the claims or the introduction of new claims. The amendments to the claims should not be construed as an acquiescence to the validity of the outstanding rejections and were done solely in the interest of expediting prosecution and allowance of the claims. Applicants reserve the right to pursue the claims as originally filed in one or more further applications.

REJECTION OF CLAIMS 70-77 UNDER 35 USC § 112, SECOND PARAGRAPH

Claims 70-77 are rejected under 35 U.S.C. § 112, second paragraph, as "being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." Specifically, the Examiner is of the opinion that the term "X-ray crystallography"

> is not defined by the claims, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Thus, x-ray crystallography is interpreted as a method having any steps involved in determining the coordinates of a crystal comprising crystallization, x-ray diffraction, computation, and phasing, for example. As it is written, it is unclear if the step requires the crystallization of claimed hydrolase. In light of specification examples, refining the crystallization condition in the presence of the hydrolase, the claims will be interpreted as having a step of crystallization with the claimed hydrolase for the examination purpose.

Applicants respectfully disagree. Notwithstanding the foregoing, solely in the interest of expediting examination and in no way acquiescing to the validity of the rejection, Applicants have amended claim 70 to recite that X-ray crystallography is performed on the crystal complex of LTA_4 hydrolase and the candidate compound ***specifically to determine the structure of the complex***. As such, Applicants submit that the claim as pending is clear and definite. Indeed, claim 70, as amended, makes clear that while crystallization of the purified LTA_4 hydrolase with bestatin is performed in step a), no further crystallization step is required. Indeed, the LTA_4 hydrolase (and bestatin) crystal is intact between steps a)-c). Upon soaking the crystal with the complementary compound in step c), the complementary compound displaces the bestatin thereby forming a complex upon which X-ray crystallography analysis is performed. In view of the foregoing and further in view of the amendments to claim 70, Applicants submit that the step of X-ray crystallography analysis is clear and definite, thereby rendering the outstanding rejection moot. Accordingly, Applicants respectfully request reconsideration and withdrawal of the foregoing rejection under 35 U.S.C. § 112, second paragraph.

REJECTION OF CLAIMS 60-77 UNDER 35 USC § 112, FIRST PARAGRAPH (WRITTEN DESCRIPTION)

The Examiner has further rejected claims 60-77 under 35 U.S.C. § 112, first paragraph as allegedly "failing to comply with the written description requirement." Specifically, the Examiner is of the opinion that

> [t]he instant claims are drawn to a method of identifying compounds or designing an inhibitor or agonist of any leukotriene A_4 hydrolase comprising: crystallizing any leukotriene A_4 hydrolase or use of cycles of X-ray crystallography, which also involves crystallizing any said enzyme and solving the structure for determining the three-dimensional coordinates, as disclosed in Claims 60 and 70. Claims 62-64 are drawn to a

> method compris[ing] crystallizing said hydrolase with any 'complexing agents' including thiolamine or hydroxamic acid. The claimed leukotriene A_4 hydrolase encompasses a very widely varying genus of enzyme includ[ing], but not limited to, any leukotriene A_4 hydrolase from any source, an enzyme having a functional equivalent of leukotriene A4 hydrolase activity with unlimited structure or any enzyme having catalytic domain similar to leukotriene A_4 hydrolase. The interpretation of the claimed genus having unlimited structure is also supported by the instant claims 65-67, 69, 73-75 and 77, which supposed [sic] to be further limiting from the independent claim 60 or 70. Claims 65-67, 69, 73-75 and 77 encompasses method comprising said amino acid residues in Claim 66 but not limited to the amino acid in SEQ ID NO:1 by the reasonable interpretation of recited term 'set forth in' or 'defined by'... Thus, any enzyme having those said amino acid residues and [that] hydrolyze any parts of leukotriene A4 molecule (including any functional equivalent) is encompassed by the instant claims...
>
> [T]he instant specification does not disclose the structure coordinates of LTA_4H as directed to the 'functional equivalent part thereof'. 'Applicant has disclosed a limited number of species; therefore, the skilled artisan cannot envision all the contemplated protein three-dimensional model and compound possibilities recited in the instant claims...' Furthermore, the instant claims 60-61 and 70-72 (reciting 'crystallizing' and 'X-ray crystallography', respectively) encompass a method of crystallizing the broad genus of claimed LTA_4 hydrolase which can not be described by the instant disclosure of by prior arts.

Pending Claims 60-62, 68, 70-72 and 76

Applicants respectfully traverse the foregoing rejection with respect to the pending claims and submit that based on the teachings in Applicants' specification as well as the general knowledge available in the art at the time of the filing of the present application, one of ordinary skill would understand that Applicants were in possession of the claimed invention. Indeed, Applicants submit that in view of their discovery of a method for crystallizing the LTA_4 hydrolase, and further in view of the teachings of the specification, one skilled in the art would appreciate that Applicants were in possession of the claimed invention at the time of filing of the present application.

Notwithstanding the foregoing, solely in the interest of expediting examination and in no way acquiescing to the validity of the Examiner's rejection, Applicants have cancelled, without prejudice, those dependent claims directed to enzymatically active domains and, further, have amended independent claims 60 and 70 such that they are directed to an LTA_4 hydrolase comprising the amino acid sequence of SEQ ID NO:1. Applicants submit that the foregoing amendments and cancellations render the outstanding rejection moot as it relates to the Examiner's assertions that "[t]he leukotriene A_4 hydrolase encompasses a very widely varying genus of enzyme includ[ing], but not limited to, any leukotriene A_4 hydrolase from any source,

an enzyme having a functional equivalent of leukotriene A_4 hydrolase activity with unlimited structure or any enzyme having catalytic domain similar to leukotriene A_4 hydrolase".

In addition, solely in the interest of expediting examination and in no way acquiescing to the validity of the outstanding rejections, Applicants have amended claims 60 and 70 to recite that the LTA_4 hydrolase is crystallized with bestatin, thereby rendering the outstanding rejection moot as it relates to "crystallizing said hydrolase with ***any 'complexing agents'***" (***emphasis added***).

Accordingly, Applicants respectfully request reconsideration and withdrawal of the outstanding rejection of the pending claims as lacking written description.

New Claims 80-86

With respect to new claims 80-86, Applicants submit that the genus of LTA_4 hydrolase molecules comprising an amino acid sequence of at least 90% identity to the amino acid sequence of SEQ ID NO:1, as set forth in each of independent claims 80 and 83, is sufficiently supported by the specification such that one skilled in the art would appreciate that Applicants were in possession of the claimed invention at the time of filing.

Disclosure of Structure, Function and Relationship Thereof

As an initial matter, Applicants direct the Examiner's attention to the standard for written description set forth in M.P.E.P. § 2163(II)(A)(3)(a):

> An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention, i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. *Enzo Biochem*, 323 F.3d at 964, 63 USPQ2d at 1613.

In view of such standard, Applicants submit that Applicants have characterized the claimed genus both structurally and functionally. Indeed, Applicants submit that the claimed genus has been defined structurally, in terms of the percent identity to a specifically disclosed amino acid sequence, and functionally, in terms of describing the molecule as having an LTA_4 hydrolase activity. Moreover, Applicants submit that the teachings of the specification teach a correlation between function and structure in accordance with the standard set forth above.

Specifically, Applicants set forth particular domains important for LTA_4 hydrolase binding and/or activity including, for example, the bestatin binding site, the leukotriene binding site, epoxide hydrolase activity, aminopeptidase activity, and the M1 region (see page 12, line 10 to page 14, line 10).

Disclosure of Particular Species of Claimed Variants

Applicants further submit that the specification teaches that such variant sequences may be designed, for example, by way of substitution, deletion and addition. Indeed, the specification provides numerous specific mutations at specific residues which may be incorporated to obtain an LTA_4 hydrolase variant of at least 90% identity to the amino acid sequence of SEQ ID NO:1 (see Tables 5-7 on page 20, line 21 to page 23, line 10).

Disclosure of Biological Assays to Confirm Function

Moreover, the specification provides various techniques to confirm that the claimed variants retain the LTA_4 hydrolase activity. For example, as set forth on page 19, line 20 to page 20, line 9, the specification teaches that various screening assays may be performed to identify LTA_4 hydrolase molecules of at least 90% identity to the amino acid sequence of SEQ ID NO:1:

> More specifically, analogue structures of LTA_4 hydrolase may be screened by their ability to catalyze a particular reaction which may be monitored by chemical[,] physical or immunological means. Furthermore, the analogue structure may be selected from its ability to produce receptor ligands or inhibitors of secondary reactions, which may be monitored directly, as examplified [*sic*] above, via binding assays, enzyme assays, chemical assays, or functional bioassays.
>
> Thus, in one embodiment, the invention relates to a method of screening, wherein one or more analogues exhibiting epoxide hydrolase activity, are screened for. Thus, such a method may be based on the data of Table 9, wherein the binding of thiolamine to LTA_4 hydrolase is shown, preferably combined with the information of Table 3 regarding the active site of LTA_4 hydrolase. In one embodiment, the invention relates to a method of screening, wherein one or more analogues exhibiting epoxide hydrolase activity, are screened for. In an alternative embodiment, the present method is used to screen for analogues exhibiting aminopeptidase activity, which method e.g. is based data concerning the binding of bestatin to LTA_4 hydrolase is used, preferably combined with the information of Table 2 regarding the active site of LTA_4 hydrolase. Thus, the present analogues will comprise a region which is essentially analogue with the regions of LTA_4 hydrolase exhibiting aminopeptidase activity, and/or analogues exhibiting epoxide hydrolase activity are selected.

Written Description Guidelines

Lastly, Applicants direct the Examiner's attention to Example 14 of the *Written Description Guidelines*. This example provides that a claim generally directed to variants of a protein having SEQ ID NO:3 "that are at least 95% identical to SEQ ID NO:3 and catalyze the reaction of A→B" with an accompanying specification that discloses a single species falling within the claimed genus, satisfies the requirements of 35 U.S.C. §112, first paragraph for written description. The rationale behind the foregoing conclusion, as presented by the *Written Description Guidelines*, is that "[t]he single species disclosed is representative of the genus because all members have at least 95% structural identity with the reference compound and because of the presence of an assay which Applicant provided for identifying all of the at least 95% identical variants of SEQ ID NO:3 which are capable of the specified catalytic activity." The Guidelines also provide that "[t]he procedures for making variants of SEQ ID NO:3 are conventional in the art and an assay is described which will identify other proteins having the claimed catalytic activity. Moreover, procedures for making variants of SEQ ID NO:3 which have 95% identity to SEQ ID NO:3 and retain its activity are conventional in the art."

Similarly, in the present case, claims 80-86 are generally directed to LTA_4 hydrolase amino acid sequences of at least 90% identity to SEQ ID NO:1. Applicants further note that the specification and the state of the art provide extensive teachings on techniques for designing such sequences and assays for identifying amino acid sequences of at least 90% identity to SEQ ID NO:1 which retain LTA_4 hydrolase activity (see, for example, page 12, line 10 to page 14 and page 19, line 10 to page 23, line 10 of the specification and the discussion above).

The indication in Example 14 of the Written Description Guidelines that the production of polypeptides which contain a ***5% variation from a specific amino acid sequence*** is routine in the art can be equated with the production of amino acid sequences which contain a ***10% variation from a specific amino acid sequence***. Indeed, the present specification and the general state of the art provide extensive guidance for making and identifying sequences of 90% identity to a specified amino acid sequence. For example, one skilled in the art would appreciate that conservative substitutions may be made at non-essential amino acid residues of the polypeptide encoded by SEQ ID NO:1, for example, by replacing residues with residues having a similar side chain. Indeed, recitation of at least 95% identity in Example 14 is merely exemplary. Similar to the rationale of Example 14, Applicants submit that the disclosed sequence (*i.e.*, SEQ ID NO:1) is representative of the genus of sequences of at least 90% identity

to the disclosed sequence and encoding a polypeptide having an LTA_4 hydrolase activity, particularly in view of the extensive teachings in the specification and the general knowledge in the art.

Accordingly, for at least the foregoing reasons, it would have been clear to one skilled in the art that Applicants were in possession of the invention, as set forth in new claims 80-86, at the time the application was filed in compliance with the 35 U.S.C. § 112, first paragraph.

REJECTION OF CLAIMS 60-77 UNDER 35 USC § 112, FIRST PARAGRAPH (ENABLEMENT)

The Examiner has further rejected claims 60-77 under 35 U.S.C. § 112, first paragraph as "not reasonably provid[ing] enablement for a method comprising: crystallizing any LTA_4 hydrolase or any enzyme having leukotriene A_4 hydrolase activity (including a functional equivalent, homolog, for example) for structure determination and screening any molecules with unlimited structure limitation."

Pending Claims 60-62, 68, 70-72 and 76

Applicants respectfully traverse this rejection and submit that based on the teachings in Applicants' specification as well as the general knowledge available in the art at the time of the filing of the present application, one of ordinary skill in the art would be able to make and use the claimed invention using only routine experimentation. Indeed, Applicants submit that in view of their discovery of a method for crystallizing the LTA_4 hydrolase, and further in view of the teachings of the specification, one skilled in the art would be capable of practicing the claimed invention without undue experimentation.

As an initial matter, Applicants note that solely in the interest of expediting examination and, in no way acquiescing to the validity of the outstanding rejections, Applicants have amended independent claims 60 and 70 such that they are directed to an LTA_4 hydrolase comprising the amino acid sequence of SEQ ID NO:1, thereby rendering the foregoing rejection moot as it relates to "crystallizing ***any LTA_4 hydrolase or any enzyme having leukotriene A_4 hydrolase activity***" (***emphasis added***).

With respect to the Examiner's assertion that the pending claims are allegedly not enabled as being directed to methods of screening or synthesizing "***any molecules with***

unlimited structure limitation," (***emphasis added***), Applicants respectfully submit that one skilled in the art would be able to practice the claimed methods without undue experimentation. Notwithstanding the foregoing, solely in the interest of expediting examination and in no way acquiescing to the validity of the Examiner's rejections, Applicants have amended claim 70 to be directed to the design of an inhibitor or agonist utilizing a ***"compound that is at least in part complementary to LTA_4 hydrolase"*** as identified using the conformational structure of the resolved crystal structure. Accordingly, to the extent that the Examiner's rejection was directed to the screening and synthesizing of ***any compound*** as an inhibitor or agonist of LTA_4 hydrolase, Applicants submit that the rejection is rendered moot by the foregoing amendment. Moreover, Applicants submit that one skilled in the art would be capable of identifying a compound that is complementary to an LTA_4 hydrolase and further practicing the claimed methods using no more than routine experimentation. Indeed, as set forth in the specification, a compound complementary to an LTA_4 hydrolase may be complementary to, for example, an enzymatically active site of the LTA_4 hydrolase including, but not limited to, an aminopeptidase binding site, the leukotriene binding site, and/or the M1 region (see page 14, line 16 to page 16, line 8). In addition, the specification teaches the particularly defined amino acid regions of such binding sites, and corresponding atomic coordinates of the crystal structure, thereby further allowing one skilled in the art to identify such complementary compounds (see page 12, line 12 to page 14, line 10 of the specification).

Moreover, the specification teaches techniques, further reflected in the pending claims, to crystallize and determine the conformational structure of an LTA_4 hydrolase crystal, thereby further allowing for one skilled in the art to identify compounds complementary to the LTA_4 hydrolase without undue experimentation. Indeed, the pending claims, as amended, are directed to specific structure based drug design techniques based on the discovery that a crystal of LTA_4 hydrolase can be achieved by employing bestatin during the crystallization procedure. Utilizing such technique, one skilled in the art would be able to follow the recited steps to identify a compound complementary to the LTA_4 hydrolase so as to design an agonist or inhibitor.

Lastly, Applicants submit that use of candidate compounds, for example, from a library of compounds, in screening methods is routine in the art. Indeed, one skilled in the art is capable of identifying candidate compounds in a library and subsequently utilizing such compounds in the claimed methods of the present invention without undue experimentation. However, it is important to note that, prior to the present invention, the inability of a skilled artisan to properly

crystallize an LTA_4 hydrolase would have prevented a skilled artisan from performing the claimed screening methods.

In view of the foregoing and further in view of the amendments presented herein, Applicants submit that the pending claims are enabled such that one skilled in the art would be able to practice the claimed invention without undue experimentation.

New Claims 80-86

With respect to new claims 80-86, Applicants submit that the genus of LTA_4 hydrolase molecules comprising an amino acid sequence of at least 90% identity to the amino acid sequence of SEQ ID NO:1, as set forth in each of independent claims 80 and 83, is sufficiently enabled such that one skilled in the art would be capable of practicing the claimed invention without undue experimentation.

As set forth above, Applicants submit that the specification and the general state of the art provide sufficient teaching to allow a person of skill in the art to make and use amino acid sequences of at least 90% identity to the amino acid sequence of SEQ ID NO:1 that retain LTA_4 hydrolase activity. First, Applicants submit that the specification provides particular domains that may be incorporated in the claimed polypeptide variants so as to allow the variants to retain LTA_4 hydrolase binding and/or activity including, for example, the bestatin binding site, the leukotriene binding site, epoxide hydrolase activity, aminopeptidase activity, and the M1 region (see page 12, line 10 to page 14, line 10). Applicants further submit that the specification teaches that such variant sequences may be designed, for example, by way of substitution, deletion and addition. Indeed, the specification provides numerous specific mutations at specific residues which may be incorporated to obtain an LTA_4 hydrolase variant of at least 90% identity to the amino acid sequence of SEQ ID NO:1 (see Tables 5-7 on page 20, line 21 to page 23, line 10). Applicants further submit that art known techniques, for example, site directed mutagenesis or PCR mediated mutagenesis, may be utilized by a skilled artisan to produce the claimed variants.

Moreover, the specification provides various techniques to confirm that the claimed variants retain the LTA_4 hydrolase activity. For example, as set forth on page 19, line 20 to page 20, line 9 (see above), the specification teaches that various screening assays may be performed to identity LTA_4 hydrolase molecules of at least 90% identity to the amino acid sequence of SEQ ID NO:1.

Lastly, Applicants once again direct the Examiner's attention to Example 14 of the *Written Description Guidelines*, which states that claims directed to sequences of 95% identity to a disclosed sequence and characterized by a particular function are sufficiently described and enabled in accordance with 35 U.S.C. § 112, first paragraph, where the specification discloses an assay for identifying such sequences. As set forth above, Applicants submit that the present specification provides extensive guidance for making and identifying such sequences (see page 12, line 10 to page 14, line 10 and see Tables 5-7 on page 20, line 21 to page 23, line 10) and further, for confirming that the claimed variants retain LTA_4 hydrolase activity (page 19, line 20 to page 20, line 9).

Applicants submit that, even though Example 14 is part of the *Written Description Guidelines* and not the *Enablement Guidelines*, this example does state explicitly that ***one skilled in the art would be able to generate a nucleotide sequence of 95% identity to another nucleotide sequence using only routine experimentation***. Specifically, the relevant section of Example 14 provides that "*[t]he procedures for making variants of SEQ ID NO:3* ***are conventional in the art*** *and an assay is described which will identify other proteins having the claimed catalytic activity. Moreover, procedures for making variants of SEQ ID NO:3 which have 95% identity to SEQ ID NO:3 and retain its activity are* ***conventional in the art***" (**Emphasis added**).

Accordingly, while the *Written Description Guidelines* generally describe the standard for satisfying the written description requirement, in this particular example, the Guidelines clearly provide guidance on the USPTO's position regarding a key question for determining whether the enablement requirement has been satisfied: would it be routine for one of skill in the art to generate a sequence with 90% or 95% identity to a specified amino acid sequence and which retains the activity of that specified nucleotide or amino acid sequence? The answer to that question, as provided by the USPTO, is: yes. The Guidelines provide that claims to sequences of 95% identity with a functional limitation are sufficiently enabled where the specification provides assays for the identification of such sequences having the requisite function. Accordingly, because it is conventional, *i.e.*, routine, to make sequences of at least 90% or 95% identity and because the instant specification provides assays for identifying nucleic acid sequences that encode a polypeptide having a LTA_4 activity, one of skill in the art would be able to make and use the claimed invention using only routine experimentation.

Lastly, Applicants submit that while Example 14 recites a claim directed to sequences of at least 95% identity to a disclosed sequence, such claim is merely exemplary. The conclusion that methods for makings sequences of at least 95% identity to a disclosed sequence are conventional in the art does not suggest that sequences of at least 90% to the disclosed sequence are not conventional in the art. Indeed, Applicants submit that, based on the extensive teachings in the specification and the general knowledge in the art, as described above, one skilled in the art would be able to produce sequences of at least 90% identity to the amino acid sequence of SEQ ID NO:1 which retain LTA_4 hydrolase activity using only routine experimentation.

In view of the foregoing and further in view of the amendments presented herein, Applicants submit that the pending claims are enabled such that one skilled in the art would be able to practice the claimed invention without undue experimentation.

CONCLUSION

In view of the foregoing remarks, reconsideration of the rejections and allowance of all pending claims is respectfully requested. If there are any remaining issues or if the Examiner believes that a telephone conversation with Applicants' Attorney would be helpful in expediting prosecution of this application, the Examiner is invited to call the undersigned at (617) 227-7400.

The Commissioner is hereby authorized to charge any deficiency in the fees paid herewith, or credit any overpayment, to Deposit Account No. 12-0080, under Order No. PVZ-006USRCE, from which the undersigned is authorized to withdraw.

Dated: December 5, 2007

Respectfully submitted,

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